

# Making Sense of TASTE

How do cells on the tongue register the sensations of **sweet**, **salty**, **sour** and **bitter**? Scientists are finding out—and discovering how the brain interprets these signals as various tastes

■ ■ ■ ■ BY DAVID V. SMITH AND ROBERT F. MARGOLSKEE

**B**ite into a gooey candy bar, and what mouth sensations do you experience? Mmmm ... chewy, sweet, creamy—with the signature, slightly bitter richness of chocolate as you close your mouth to swallow and the aroma wafts up into your nasal passages. Indeed, smell is an important component of flavor, as anyone with a severe head cold can testify.

Flavor is a complex mixture of sensory input composed of taste (gustation), smell (olfaction) and the tactile sensation of food as it is being munched, a characteristic that food scientists often term “mouthfeel.” Although people may use the word “taste” to mean “flavor,” in the strict sense it is applicable only to the sensations arising from specialized taste cells in the mouth. Scientists generally describe human taste perception in terms of four qualities: saltiness, sourness, sweetness and bitterness. Some researchers have suggested, however, that other catego-

ries exist as well—most notably umami, the sensation elicited by glutamate, one of the 20 amino acids that make up the proteins in meat, fish and legumes. Glutamate also serves as a flavor enhancer in the form of the food additive monosodium glutamate (MSG).

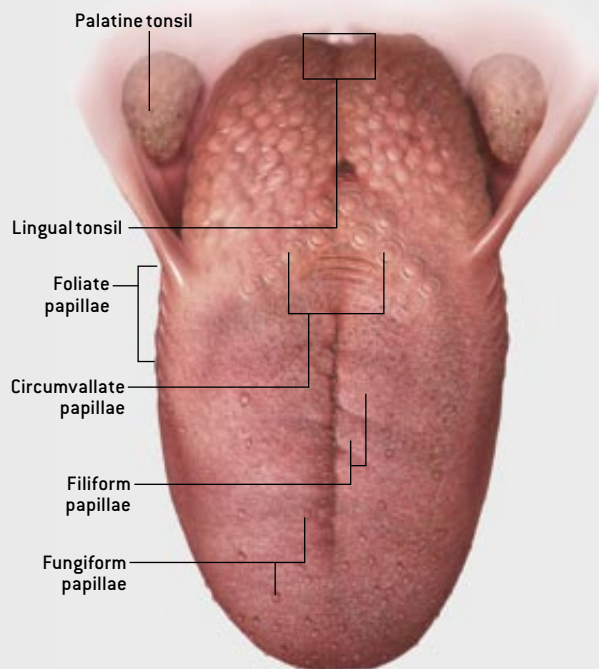
Within the past few years, researchers have made strides in elucidating exactly how taste works. Neurobiologists, including one of us (Margolskee), have identified proteins that are crucial for taste cells to detect sweet and bitter chemicals and have found that they are very similar to related proteins involved in vision. Other scientists, including the other one of us (Smith) and his co-workers, have obtained evidence that nerve cells, or neurons, in the brain can respond to more than one type of taste signal, just as those that process visual stimuli from the retinas can react to more than one color. The findings illuminate what has historically been one of the least understood senses.

## Anatomy of Taste

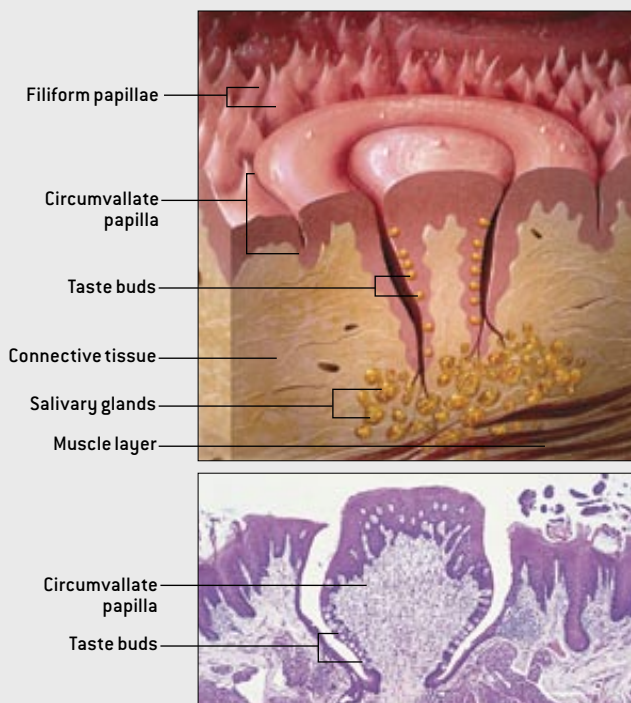
These illustrations show the four types of projections called papillae on the human tongue, the structure of one papilla—the circumvallate papilla—and details of human taste buds. (The circumvallate papilla and the taste bud are shown as both diagrams and micrographs.) Only the circumvallate, foliate and fungiform papillae bear taste buds. The filiform papillae lack taste buds but are important for tactile sensation. During

chewing, chemicals from food called tastants enter the taste pores of taste buds, where they interact with molecules on fingerlike processes called microvilli on the surfaces of specialized taste cells. The interactions trigger electrochemical changes in the taste cells that cause them to transmit signals that ultimately reach the brain. The impulses are interpreted, together with smell and other sensory input, as flavors.

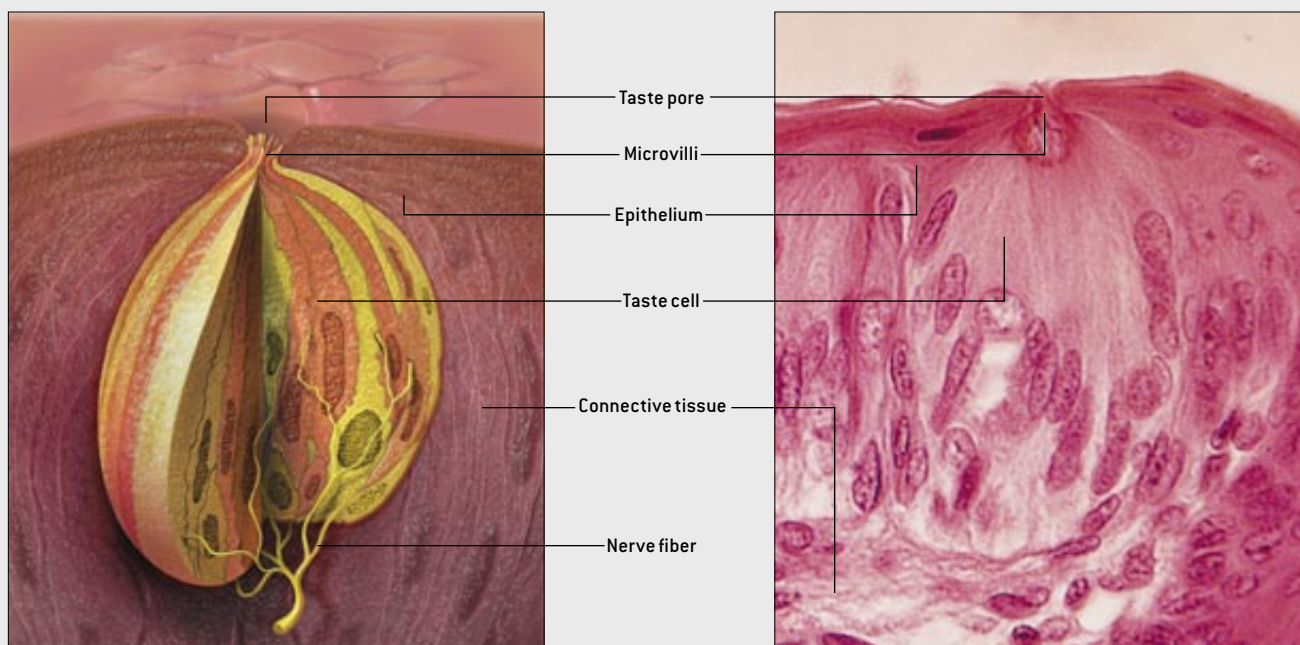
Tongue



Circumvallate Papilla



Taste Bud



KEITH KASNOT (illustrations); BIOPHOTO ASSOCIATES/PHOTO RESEARCHERS, INC. (papilla); PHOTO RESEARCHERS, INC. (taste buds)



## The Taste Detectors

TASTE CELLS LIE within specialized structures called taste buds, which are situated predominantly on the tongue and soft palate. The majority of taste buds on the tongue are located within papillae, the tiny projections that give the tongue its velvety appearance. (The most numerous papillae on the tongue—the filiform, or threadlike, ones—lack taste buds, however, and are involved in tactile sensation.) Of those with taste buds, the fungiform (“mushroomlike”) papillae on the front part of the tongue are most noticeable; these contain one or more taste buds. The fungiform papillae appear as pinkish spots distributed around the edge of the tongue and are readily visible after taking a drink of milk or placing a drop of food coloring on the tip of the tongue. At the back of the tongue are roughly 12 larger taste bud-containing papillae called the circumvallate (“wall-like”) papillae, which are distributed in the shape of an inverted V. Taste buds are also located in the foliate (“leaflike”) papillae, small trenches on the sides of the rear of the tongue.

Taste buds are onion-shaped structures of between 50 and 100 taste cells, each of which has fingerlike projections called microvilli that poke through an opening at the top of the taste bud called the taste pore. Chemicals from food termed tastants dissolve in saliva and contact the taste cells through the taste pore. There they interact either with proteins on the surfaces of the cells known as taste receptors or with porelike proteins called ion channels. These interactions cause electrical changes in the taste cells that trigger them to send chemical signals that ultimately result in impulses to the brain.

The electrical changes in the taste cells that prompt signals to the brain are based on the varying concentrations of charged atoms, or ions. Taste cells, like neurons, normally have a net negative charge internally and a net positive charge externally. Tastants alter this state of affairs by using various means to increase the concentration of positive ions inside taste cells, eliminating the charge difference [see box on

next two pages]. Such depolarization causes the taste cells to release tiny packets of chemical signals called neurotransmitters, which prompt neurons connected to the taste cells to relay electrical messages.

But studies of animals and people show there is not always a strict correlation between taste quality and chemical class, particularly for bitter and sweet tastants. Many carbohydrates are sweet, for instance, but some are not. And very disparate types of chemicals can evoke the same sensation: people deem chloroform and the artificial sweeteners aspartame and saccharin sweet even though their chemical structures have nothing in common with sugar. The compounds that elicit salty or sour tastes are less diverse and are typically ions.

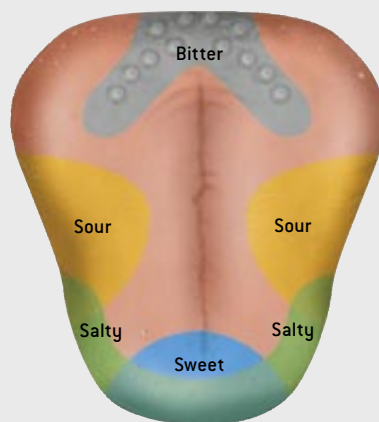
The chemicals that produce salty and sour tastes act directly through ion channels, whereas those responsible for sweet and bitter tastes bind to surface receptors that trigger a bucket brigade of signals to the cells' interiors that ultimately results in the opening and closing of ion channels. In 1992 Margolskee and his colleagues Susan K. McLaugh-

lin and Peter J. McKinnon identified a key member of this bucket brigade. They named the molecule “gustducin” because of its similarity to transducin, a protein in retinal cells that helps to convert, or transduce, the signal of light hitting the retina into an electrical impulse that constitutes vision.

Gustducin and transducin are both so-called G-proteins, which are found stuck to the undersides of many different types of receptors. (The name “G-protein” derives from the fact that the activity of such proteins is regulated by a chemical called guanosine triphosphate, GTP.) When the right tastant molecule binds to a taste cell receptor, like a key in a lock, it prompts the subunits of gustducin to split apart and carry out biochemical reactions that ultimately open and close ion channels and make the cell interior more positively charged.

In 1996 Margolskee and Gwendolyn T. Wong and Kimberley S. Gannon used mice they genetically engineered to lack one of gustducin's three subunits to demonstrate that the G-protein is crucial for tasting bitter and sweet compounds. Unlike normal mice, the al-

### The “Taste Map”: All Wrong



**Outdated “tongue map”** has continued to appear in textbooks even though it was based on a misinterpretation of research done in the 19th century.

that contain taste buds. At present, we have no evidence that any kind of spatial segregation of sensitivities contributes to the neural representation of taste quality, although there are some slight differences in sensitivity across the tongue and palate, especially in rodents.

One of the most dubious “facts” about taste—and one that is commonly reproduced in textbooks—is the oft-cited but misleading “tongue map” showing large regional differences in sensitivity across the human tongue. These maps indicate that sweetness is detected by taste buds on the tip of the tongue, sourness on the sides, bitterness at the back and saltiness along the edges.

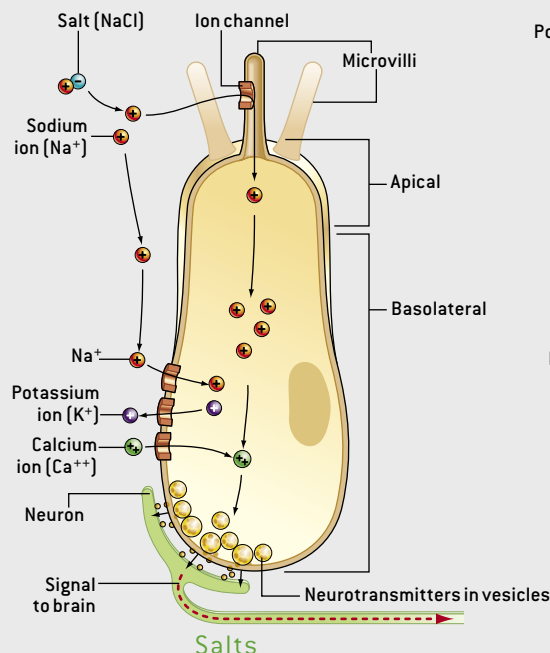
Taste researchers have known for many years that these tongue maps are wrong. The maps arose early in the 20th century as a result of a misinterpretation of research reported in the late 1800s, and they have been almost impossible to purge from the literature.

In reality, all qualities of taste can be elicited from all the regions of the tongue

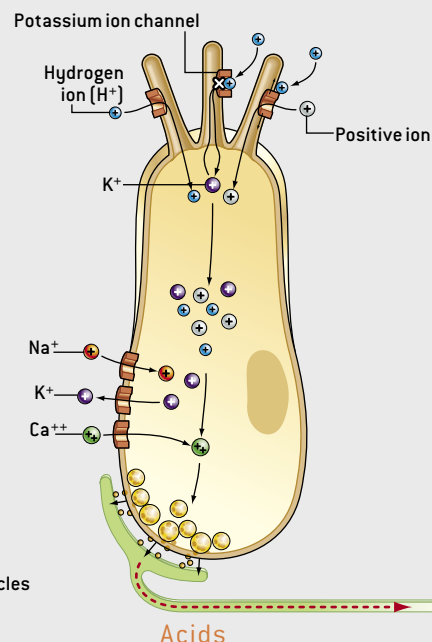
—D.V.S. and R.F.M.

## Taste Fundamentals

The stimuli that the brain interprets as the basic tastes—salty, sour, sweet, bitter and, possibly, umami—are registered via a series of chemical reactions in the taste cells of the taste buds. The five biochemical pathways underlying each taste quality are depicted here in separate taste cells solely for clarity. In reality, individual taste cells are not programmed, or “tuned,” to respond to only one kind of taste stimulus.



**Salts**, such as sodium chloride (NaCl), trigger taste cells when sodium ions ( $\text{Na}^+$ ) enter through ion channels on microvilli at the cell's apical, or top, surface. [Sodium ions can also enter via channels on the cell's basolateral, or side, surface.] The accumulation of sodium ions causes an electrochemical change called depolarization that results in calcium ions ( $\text{Ca}^{++}$ ) entering the cell. The calcium, in turn, prompts the cell to release chemical signals called neurotransmitters from packets known as vesicles. Nerve cells, or neurons, receive the message and convey a signal to the brain. Taste cells repolarize, or “reset,” themselves in part by opening potassium ion channels so that potassium ions ( $\text{K}^+$ ) can exit.



**Acids** taste sour because they generate hydrogen ions ( $\text{H}^+$ ) in solution. Those ions act on a taste cell in three ways: by directly entering the cell; by blocking potassium ion channels on the microvilli; and by binding to and opening channels on the microvilli that allow other positive ions to enter the cell. The resulting accumulation of positive charges depolarizes the cell and leads to neurotransmitter release.

tered mice did not prefer sweet foods or avoid bitter substances: they did not avidly drink highly sweetened water and instead drank solutions of very bitter compounds as readily as they did plain water. Moreover, these mice were indifferent to the umami taste of glutamate. The researchers also showed that key nerves in the mice lacking gustducin had a reduced electrical response to sweet, bitter and umami tastants but could still respond to salts and acidic compounds.

In 2000 two groups of scientists—one led jointly by Charles S. Zuker of the Howard Hughes Medical Institute (HHMI) at the University of California, San Diego, and by Nicholas J. Ryba of the National Institute of Dental and Craniofacial Research and the other led by HHMI investigator Linda B. Buck of Harvard Medical School—identified in mice and humans the actual receptors that bind to bitter tastants and activate gustducin. The teams found that the so-called T2R/TRB receptors are part of a

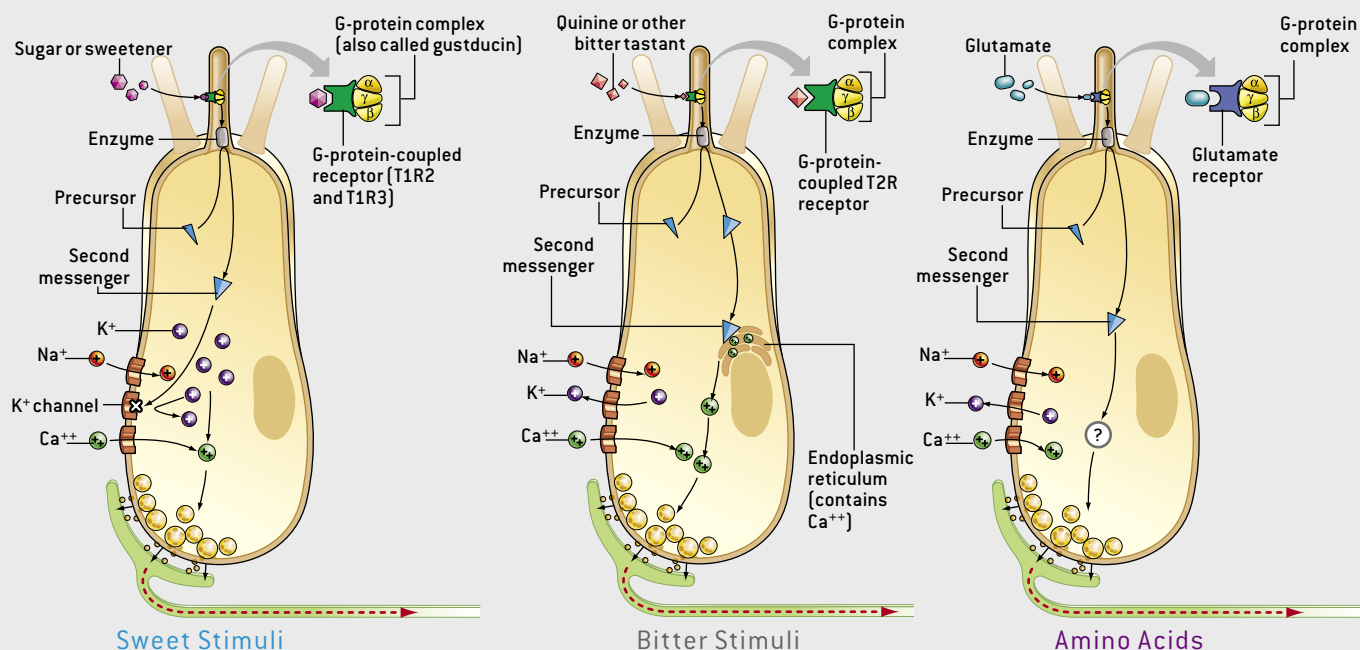
family of related receptors that is estimated to have between 25 and 30 members.

Zuker and Ryba's group inserted the genes that encode two of these mouse taste receptors, mT2R5 and mT2R8, into cells grown in the laboratory and found that the engineered cells became activated when they were exposed to two bitter compounds. The researchers noted that in particular strains of mice a specific version of the gene for mT2R5 tended to be handed down along with the ability to sense the bitterness of the antibiotic cycloheximide, a further indication that the genes for the T2R receptors were responsible for detecting bitter substances. During the past few years, Wolfgang Meyerhof and his colleagues at the German Institute of Human Nutrition have determined for several T2R receptors which bitter compounds they respond to.

In 2001 several research groups, including that of Margolskee, identified T1R3, a novel type I taste receptor.

Margolskee's colleague Marianna Max mapped T1R3 to the *Sac* (saccharin sweet taste) locus in the mouse genome. A specific sequence variation of the T1R3 gene was shown to determine the high preference for sugars, saccharin and other sweeteners displayed by so-called taster strains of mice. Margolskee and his colleague Sami Damak genetically altered taster mice to lack T1R3 to determine that this taste receptor was essential to a mouse's ability to taste sweet compounds.

Researchers are also studying receptors that might be responsible for the taste Japanese scientists call umami, which loosely translates into “meaty” or “savory.” In 1998 Nirupa Chaudhari and Stephen D. Roper of the University of Miami isolated a receptor from rat tissue that binds to the amino acid glutamate and proposed that it underlies the umami taste. Other receptors have also been implicated in the taste of glutamate. The T1R3 receptor turns out to



**Sweet stimuli**, such as sugar or artificial sweeteners, do not enter taste cells but trigger changes within the cells. They bind to dimeric receptors [T1R2 and T1R3] on a taste cell's surface that are coupled to molecules named G-proteins. This prompts the subunits ( $\alpha$ ,  $\beta$  and  $\gamma$ ) of the G-proteins to split into  $\alpha$  and  $\beta\gamma$ , which activate a nearby enzyme. The enzyme then converts a precursor within the cell into so-called second messengers that close potassium channels indirectly.

**Bitter stimuli**, such as quinine, act through G-protein-coupled T2R receptors and second messengers. In this case, however, the second messengers cause the release of calcium ions from the endoplasmic reticulum. The resulting buildup of calcium in the cell leads to depolarization and neurotransmitter release.

**Amino acids**—such as glutamate, which stimulates the umami taste—are known to bind to G-protein-coupled dimeric receptors [T1R1 and T1R3] and to activate second messengers. But the intermediate steps between the second messengers and the release of packets of neurotransmitters are unknown.

be important for the umami taste as well as for the sweet taste. T1R3 typically functions in a “heterodimeric” combination with other related T1R receptors. The combination of T1R3 plus T1R1 responds to glutamate, whereas the combination of T1R3 plus T1R2 responds to sweet compounds. Mice lacking T1R3 not only are insensitive to sugars but also lose their preference for glutamate. Other receptors, however, are involved in the avoidance of high concentrations of glutamate.

But taste is much more than just receptors for the four (or five) primary tastants and the biochemical interactions they induce in taste cells. Although we tend to think of taste information in terms of the qualities of salty, sour, sweet and bitter, the taste system represents other attributes of chemical stimuli as well. We sense the intensity of a taste and whether it is pleasant, unpleasant or neutral. Neurons in the taste pathway record these attributes simultaneously,

much as those in the visual system represent shape, brightness, color and movement. Taste neurons often respond to touch and temperature stimuli, too.

## Taste in the Brain

SCIENTISTS HAVE gone back and forth on whether individual neurons are “tuned” to respond only to a single tastant such as salt or sugar—and therefore signal only one taste quality—or whether the activity in a given neuron contributes to the neural representation of more

than one taste. Studies by Smith and those of several other colleagues show that both peripheral and central gustatory neurons typically respond to more than one kind of stimulus. Although each neuron responds most strongly to one tastant, it usually also generates a response to one or more other stimuli with dissimilar taste qualities.

How then can the brain represent various taste qualities if each neuron responds to many different-tasting stimuli? Many researchers believe it can do so

## THE AUTHORS

**DAVID V. SMITH** and **ROBERT F. MARGOLSKEE** approach the study of taste from complementary angles. Smith's training is in psychobiology and neurophysiology. He is Simon R. Bruesch Professor and chairman of the department of anatomy and neurobiology at the University of Tennessee College of Medicine. He earned his Ph.D. from the University of Pittsburgh and received postdoctoral training at the Rockefeller University. Margolskee's training is in molecular neurobiology and biochemistry. He is an associate investigator of the Howard Hughes Medical Institute and a professor of physiology and biophysics and of pharmacology at the Mount Sinai School of Medicine, where he has been since 1996. He received his M.D. and Ph.D. in molecular genetics from the Johns Hopkins School of Medicine and did postdoctoral research in biochemistry at Stanford University. He founded the biotechnology company Linguagen in Paramus, N.J.

only by generating unique patterns of activity across a large set of neurons.

This thinking represents a “back to the future” movement among taste researchers. The very first electrophysiological studies of gustatory sensory neurons, done in the early 1940s by Carl Pfaffmann of Brown University, demonstrated that peripheral neurons are not specifically responsive to stimuli representing a single taste quality but instead record a spectrum of tastes. Pfaffmann suggested that taste quality might be represented by the pattern of activity across gustatory neurons because the activity of any one cell was ambiguous. But in the 1970s and 1980s several scientists began to accumulate data indicating that individual neurons are tuned maximally for one taste. They interpreted this as evidence that activity in a particular type of cell represented a given taste quality—an idea they called the labeled-line hypothesis. According to this idea, activity in neurons that respond best to sugar would signal “sweetness,” activity in those that respond best to acids would signal “sourness,” and so on [see box on page 92].

As early as 1983 Smith and his colleagues Richard L. Van Buskirk, Joseph

B. Travers and Stephen L. Bieber demonstrated that the same cells that others had interpreted as labeled lines actually defined the similarities and differences in the patterns of activity across taste neurons. This suggested that the same neurons were responsible for taste-quality representation, whether they were viewed as labeled lines or as critical parts of an across-neuron pattern. These investigators further demonstrated that the neural distinction among stimuli of different qualities depended on the simultaneous activation of different cell types, much as color vision depends on the comparison of activity across photoreceptor cells in the eye. These and other considerations have led us to favor the idea that the patterns of activity are key to coding taste information.

Scientists now know that things that taste alike evoke similar patterns of activity across groups of taste neurons. What is more, they can compare these patterns and use multivariate statistical analysis to plot the similarities in the patterns elicited by various tastants. Taste researchers have generated such comparisons for gustatory stimuli from the neural responses of hamsters and rats. These cor-

respond very closely to similar plots generated in behavioral experiments, from which scientists infer which stimuli taste alike and which taste different to animals. Such data show that the across-neuron patterns contain sufficient information for taste discrimination.

When we block the activity of certain neuron groups, the behavioral discrimination among stimuli—that between the table salt sodium chloride and the salt substitute potassium chloride, for example—is disrupted. This result can be shown directly after treating the tongue with the diuretic drug amiloride. Thomas P. Hettinger and Marion E. Frank of the University of Connecticut Health Sciences Center demonstrated that amiloride reduces the responses of some types of peripheral gustatory neurons but not others. It blocks sodium channels on the apical membranes of taste receptor cells—the membranes that are closest to the opening of taste pores—and exerts its influence primarily on neurons that respond best to sodium chloride.

Smith and his colleague Steven J. St. John demonstrated that treatment with amiloride eliminates the differences in the across-neuron patterns between so-

## What We Learn from Yummy and Yucky

**S**ensory information from taste cells is critical for helping us to detect and respond appropriately to needed nutrients. The sweet taste of sugars, for example, provides a strong impetus for the ingestion of carbohydrates. Taste signals also evoke physiological responses, such as the release of insulin, that aid in preparing the body to use the nutrients effectively. Humans and other animals with a sodium deficiency will seek out and ingest sources of sodium. Evidence also indicates that people and animals with dietary deficiencies will eat foods high in certain vitamins and minerals.

Just as important as ingesting the appropriate nutrients is not ingesting harmful substances. The universal avoidance of intensely bitter molecules shows a strong link between taste and disgust. Toxic compounds, such as strychnine and other common plant alkaloids, often have a strong bitter taste. In fact, many plants have evolved such compounds as a protective mechanism against foraging animals. The sour taste of spoiled foods also contributes to their avoidance. All animals, including humans, generally reject acids and bitter-tasting substances at all but the weakest concentrations.

The intense reactions of pleasure and disgust evoked by

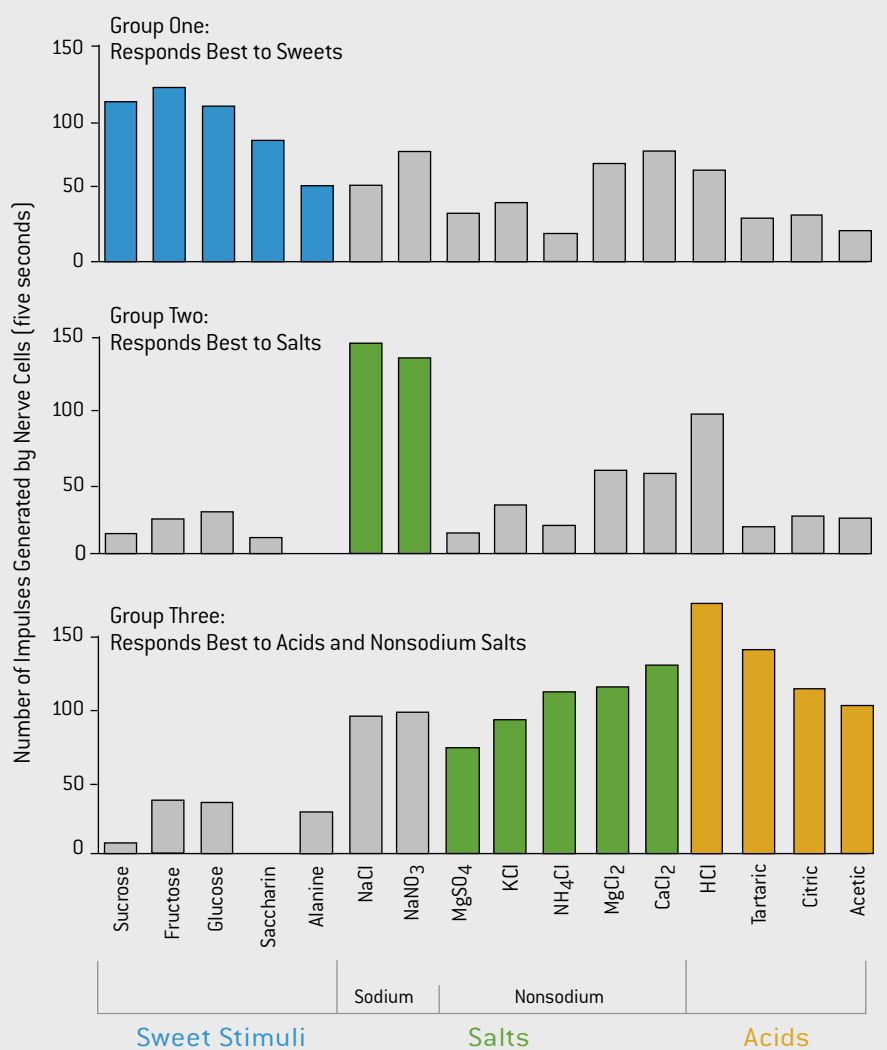
sweet and bitter substances appear to be present at birth and to depend on neural connections within the lower brain stem. Animals with their forebrains surgically disconnected and anencephalic human newborns (those lacking a forebrain) show facial responses normally associated with pleasure and disgust when presented with sweet and bitter stimuli, respectively.

The strong link between taste and pleasure—or perhaps displeasure—is the basis of the phenomenon of taste-aversion learning. Animals, including humans, will quickly learn to avoid a novel food if eating it causes, or is paired with, gastrointestinal distress. Naturally occurring or experimentally induced taste-aversion learning can follow a single pairing of tastant and illness, even if there is a gap of many hours between the two. One side effect of radiation treatments and chemotherapy in cancer patients is loss of appetite; much of this is caused by conditioned taste aversions resulting from the gastrointestinal discomfort produced by these treatments. This mechanism has also made it extremely difficult to devise an effective poison for the control of rats, which are especially good at making the association between novel tastants and their physiological consequences.

—D.V.S. and R.F.M.

## Measuring the Preferences of Taste Neurons

Nerve cell activity tests demonstrate that taste neurons can respond to different types of taste stimuli—be they sweet, salty, sour or bitter—although the cells usually respond most strongly to one type. (Bitter and umami stimuli are not shown.)



dium chloride and potassium chloride in rats. It also disrupts the rats' ability to discriminate behaviorally between these stimuli, as shown by Alan C. Spector and his colleagues at the University of Florida. Reducing the activity in other cell types also abolishes the differences in the across-neuron patterns evoked by these salts, but in a completely different way. These studies showed that it is not a specific cell type that is responsible for taste discrimination but a comparison in the activity across cells. Thus, taste discrimination depends on the relative activity of different neuron types, each of which must contribute to the overall

pattern of activity for an individual to distinguish among different stimuli.

Because taste neurons are so widely responsive, neurobiologists must compare the levels of activity of a range of neurons to get an idea of what sensation they are registering. No single neuron type alone is capable of discriminating

among stimuli of different qualities, because a given cell can respond the same way to disparate stimuli, depending on their relative concentrations. In this sense, taste is like vision, in which three types of photoreceptors respond to light of a broad range of wavelengths to allow us to see the myriad hues of the rainbow. It is well known that the absence of one of these photoreceptor pigments disrupts color discrimination, and this disruption extends well beyond the wavelengths to which that receptor is most sensitive. That is, discrimination between red and green stimuli is disrupted when either the "red" or the "green" photopigment is absent.

Although this analogy with color vision provides a reasonable explanation for neural coding in taste, researchers continue to debate whether individual neuron types play a more significant role in taste coding than they do in color vision. Scientists are also questioning whether taste is an analytic sense, in which each quality is separate, or a synthetic sense like color vision, in which combinations of colors produce a unique quality. A challenge to elucidating neural coding in this system is the precise determination of the relation between the activity in these broadly tuned neurons and the sensations evoked by taste mixtures.

These diverse experimental approaches to investigating the gustatory system—ranging from isolating taste cell proteins to studying the neural representation of taste stimuli and the perception of taste quality in humans—are coming together to provide a more complete picture of how the taste system functions. This knowledge will spur discoveries of new artificial sweeteners and improved substitutes for salt and fat—in short, the design of more healthful foods and beverages that taste great, too. **SA**

### MORE TO EXPLORE

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EDWARD BELL



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